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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,732	12/19/2001	William M. Pardridge	0180.0029	8416

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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,732	PARDRIDGE, WILLIAM M.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 23-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed December 27, 2004. Amendments were made to the claims.

Claims 1-10 and 23-29 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed September 22, 2004, that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action and/or sets forth new rejections that are necessitated by amendment, this Office Action is made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 23-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for the reasons set forth in the previous Office Action**.

Response to Arguments Concerning Claim Rejections - 35 USC § 112

Applicant's arguments filed December 27, 2004 have been fully considered but they are not persuasive. Applicant provides the following grounds of traversal:

1. Applicant argues that the amendment to the claim to include "delivering an eye-specific therapeutic gene to an ocular cell" indicates that the composition is directed to solving a "delivery" problem (see for example page 6, second paragraph of Applicant's Remarks), and not a gene therapy problem. Therefore, Applicant contends the asserted utility is not "gene therapy," but an issue of "gene delivery" (see for example page 6, third paragraph of Applicant's Remarks).

2. Applicant argues that the gene to be encapsulated within the liposome is only one of four elements of the composition, and that the use of the term 'therapeutic agent' "should not be used to imply an asserted utility of 'gene therapy'" (see for example pages 6-7, bridging paragraph of Applicant's Remarks).

3. Applicant argues that the teachings of Verma with regard to the instant invention are irrelevant. This is because "Applicant's liposomes include conjugation agents that render the liposome anionic; Verma, in contrast, only teaches that cationic liposomes are deficient in the ability to deliver and sustain the expression of a gene (see for example page 7, bottom paragraph of Applicant's Remarks).

4. Applicant argues that the delivery and expression of β-galactosidase represents an *in vivo* exemplification of the ability to use the claimed invention, as opposed to the Office's assertion that there are no exemplifications for using the claimed composition. Furthermore, Applicant asserts that the delivery and expression of β-galactosidase can easily be extended to include the

delivery and expression of therapeutic genes (see for example pages 8-9, bridging paragraph of Applicant's Remarks).

5. Applicant argues that their gene expression is non-transitory, and supports this with data uncovered in Rhesus monkeys (see for example page 9 of Applicant's response). Specifically, Applicant argues that the time dependent loss of gene expression is reversible due to the lack of integration, and that this "reversibility of expression" is by design so as to avoid the possibility of insertional mutagenesis (see for example page 9 of Applicant's response).

6. Applicant concludes that the instant invention is not unpredictable, as asserted by the Office. This is because the instant invention addresses the concerns of Verma by using anionic liposomes as it relates to delivery of genes to cells (see for example page 10, bottom paragraph of Applicant's Remarks), and because it is beyond the scope of the invention to enable therapy (see for example page 12 of Applicant's Remarks).

Applicant's traversal has been fully considered, but is not found convincing for the following reasons:

1. The amendment to include the terminology "delivering an eye-specific therapeutic gene to an ocular cell" is merely an intended use, and carries no patentable weight because the claim is not a method claim. The language that is integral to determining the patentability of the claim are those terms that convey functional language on the product. One such term is "a gene that expresses a therapeutic agent." This term conveys on the liposome functional language regarding the therapeutic value of the gene contained within the liposome, and therefore the liposome itself. Because this functional language remains in the claim, this function must meet

the enablement standards. Thus, in contrast to Applicant's assertion, the claim does read on "gene therapy." This is especially true given the asserted utility of gene therapy that is set forth in the specification. As set forth in the previous Office Action, the instant invention is not enabled for such a use.

2. The fact that the therapeutic agent is only one of four elements to the claim does not exempt it from satisfying the enablement standard. In order to make and use the claimed invention, the skilled artisan must be able to make and use the whole claimed invention, and not merely three-fourths of the invention. It is again reiterated that the Office cannot simply ignore the functional language "therapeutic agent," as such language has a clear meaning that the agent have a therapeutic effect. Thus, the liposome must also have a gene therapy function, given the functional language of the agent it is designed to deliver.

3. It is first noted that there is nothing in the claim to indicate that the instantly claimed liposome is *only* anionic in nature. Indeed, Applicant argues that the claimed invention "includes" conjugation agents that convey an anionic nature upon the claimed liposome; however, there is no indication that the full scope of conjugation agents that are used "excludes" agents that do not convey an anionic nature upon the claimed liposome. In other words, as the claim currently reads, it includes both anionic and cationic liposomes, without any clear exclusion of a particular type of liposome.

It is also important to note that the use of cationic liposomes is only one issue raised by Verma. The cationic versus anionic nature of the liposome that is claimed does not address any of the other major drawbacks to gene therapy; in particular the inability to maintain expression at a therapeutic level. Thus, even if the claimed liposomes were solely anionic, this still would not

address all of the concerns raised by Verma as it regards gene therapy as a whole. This issue of maintaining therapeutic levels of expression will be addressed below.

4 and 5. The expression of β-galactosidase (or another reporter gene) cannot easily be extended to a "therapeutic agent," as suggested by Applicant. If this were true, gene therapy issues such as maintaining therapeutic levels of gene expression and determining how much of a therapeutic agent to deliver to target cells would not be crippling issues to gene therapy, as reported by Verma. The ability to express a marker for 48 hours does not translate in the ability to consistently target and express the proper, therapeutic amounts of a gene in the cells of a living organism. This is made clear in Applicant's own arguments about the expression of a marker gene in Rhesus monkeys, discussed below.

Applicant argues that their expression is not transitory; however, Applicant clearly states that, in their experiments with Rhesus monkeys that gene expression was lost over time. This is *exactly* the problem raised in Verma, where it is clearly indicated that continued expression at a therapeutic level is a major issue hindering the effectiveness of gene therapy. Applicant suggests that this decrease in expression is designed to prevent mutagenesis of the target cell; however, this does not address how the therapeutic nature of the agent is maintained in the absence of its expression, suggesting that the therapeutic value of the liposome is lost over time. It is also important to note that this issue appropriately highlights a major issue with gene therapy; the balance between maintaining expression at a therapeutic level while not adversely affecting a normal cellular process has been unobtainable. Thus, it is clear that Applicant's invention has not overcome the issues raised by Verma concerning the enablement of gene therapy because they cannot maintain the expression of a gene at a therapeutic level.

6. In conclusion, the invention is still unpredictable. First, the use of the term "therapeutic agent" contains functional language that must be met within the claim; i.e., the claimed liposome must be therapeutic as it contains a therapeutic agent. Therefore, the claimed liposome must be enabled for purposes of gene therapy, which are disclosed in the specification as the utility for liposomes comprising a therapeutic agent. Furthermore, the use of anionic liposomes, even if it were a clear limitation of the claims, does not address all of the concerns surrounding gene therapy, as disclosed in the Verma reference provided in the previous Office Actions. These issues include the maintained expression of a gene at a therapeutic level; indeed, Applicant's own arguments indicate that, *in vivo*, expression of their gene was shown to decrease with time, establishing and accentuating the issues raised by Verma and the Office. Thus, the invention as claimed continues to read on gene therapy, and remains deficient in enabling such therapy, despite Applicant's arguments to the contrary.

Allowable Subject Matter

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER